Ex vivo human carotid artery bifurcation stenting: Correlation of lesion characteristics with embolic potential

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Purpose: To develop an ex vivo human carotid artery stenting model that can be used for the quantitative analysis of risk for embolization associated with balloon angioplasty and stenting and to correlate this risk with lesion characteristics to define lesions suitable for balloon angioplasty and stenting.

Methods: Specimens of carotid plaque (n = 24) were obtained circumferentially intact from patients undergoing standard carotid endarterectomy. Carotid lesions were prospectively characterized on the basis of angiographic and duplex findings before endarterectomy and clinical findings. Specimens were encased in a polytetrafluoroethylene wrap and mounted in a flow chamber that allowed access for endovascular procedures and observations. Balloon angioplasty and stenting were performed under fluoroscopic guidance with either a Palmaz stent or a Wallstent endoprosthesis. Ex vivo angiograms were obtained before and after intervention. Effluent from each specimen was filtered for released embolic particles, which were microscopically examined, counted, and correlated with various plaque characteristics by means of multivariate analysis.

Results: Balloon angioplasty and stenting produced embolic particles that consisted of atherosclerotic debris, organized thrombus, and calcified material. The number of embolic particles detected after balloon angioplasty and stenting was not related to preoperative symptoms, sex, plaque ulceration or calcification, or artery size. However, echolucent plaques generated a higher number of particles compared with echogenic plaques ($p < 0.01$). In addition, increased lesion stenosis also significantly correlated with the total number of particles produced by balloon angioplasty and stenting ($r = 0.55$). Multivariate analysis revealed that these two characteristics were independent risk factors.

Conclusions: Echolucent plaques and plaques with stenosis ≥90% produced a higher number of embolic particles and therefore may be less suitable for balloon angioplasty and stenting. This ex vivo model can be used to identify high-risk lesions for balloon angioplasty and stenting and can aid in the evaluation of new devices being considered for carotid balloon angioplasty and stenting. (J Vasc Surg 1998; 27:463-71)

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Balloon angioplasty and stenting have been widely used to treat patients with coronary and peripheral arterial occlusive disease.[1,2] Despite the relative safety of the procedure, complications of balloon angioplasty and stenting, including embolic events, have been reported to occur at all anatomic sites.[2,3] The use of balloon angioplasty and stenting in the management of stenosis at the carotid bifurcation has been limited, primarily because of the availability of excellent surgical therapy and because of concern about embolic stroke.[4]

The morphologic characteristics of plaques at the carotid bifurcation have been extensively studied. The complex histopathologic features of these lesions also have been well described,[5-7] which has ham-

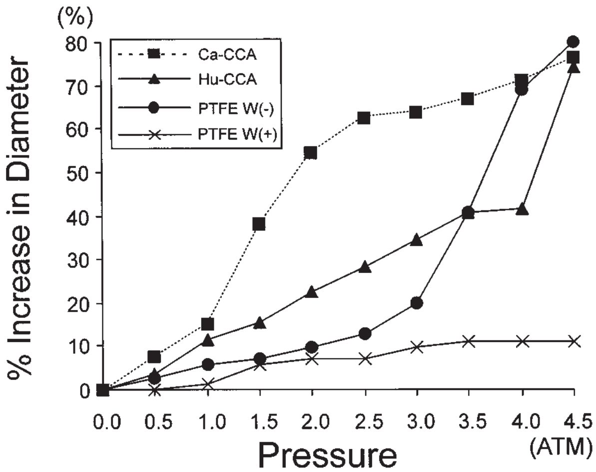

Fig. 1. Elasticity of human carotid artery adventitia. Data are expressed as mean of triplicate studies. *Ca-CCA,* canine common carotid artery; *Hu-CCA,* human common carotid artery; *PTFE W(-),* ePTFE graft without outer reinforcing wrap; *PTFE W(+),* ePTFE grafting with outer reinforcing wrap.

pered the development of animal models that can be used to evaluate embolic events after endovascular intervention.

We developed an ex vivo human carotid stenting model to quantitatively analyze the risk for embolic events associated with balloon angioplasty and stenting.[8,9] This model was used to correlate embolic risk with lesion characteristics in the hope that this model would aid in the selection of appropriate lesions for management with this technique.

METHODS

Elasticity of human carotid artery adventitia. To find a material that has mechanical properties similar to those of human carotid artery adventitia, a study of elasticity was performed on different materials, including human carotid artery adventitia (n = 3), canine carotid artery adventitia (n = 3), expanded polytetrafluoroethylene (ePTFE) graft (n = 3) (7 mm ePTFE graft; W. L. Gore and Associates, Flagstaff, Ariz.), and ePTFE graft with the outer reinforcing wrap removed (n = 3). Carotid arteries were obtained from patients whose bodies were examined by means of postmortem studies. None of these specimens had marked carotid atherosclerotic disease. Each of the materials was cut to 4 cm in length and dilated with a balloon (Ultra-thin; Medi-tech, Watertown, Mass.) that was 50% larger in diameter than the diameter of the tested material at rest. The balloon was inflated and the outer diameter of the material was measured under a dissecting microscope (magnification, 3×) at every 0.5 atm increase in inflating pressure (Fig. 1). The elasticity of a given material can be described according to the modulus of elasticity, which is an innate property of the material that determines how strain responds to stress.[10] We calculated the modulus of each material using the following equation: Modulus (of elasticity) = Stress ÷ Strain = P ÷ (Δd / d), where P is the pressure exerted on the arterial wall, Δd is the change in diameter measured in the blood vessel, and d is the original diameter of the blood vessel.

The stress of a vessel is reflected in the pressure on the artery. Strain is obtained by dividing the change in diameter size by the original arterial diameter. Within its elastic limit, an artery exhibits a linear relation between stress and strain. In our experiment, stress and strain were determined as the averages of three tests from three individual blood vessels or materials (Fig. 1). Fig. 1 shows that stress and strain follow a relatively linear relation when pressure is less than 3 atm. Accordingly, the modulus of elasticity was calculated for each of the materials at 3 atm by means of the foregoing equation. The moduli for canine, human, ePTFE graft, and ePTFE graft with outer reinforcing wrap removed were 4.6, 8.6, 15.0, and 30.3. Therefore we used ePTFE with the outer reinforcing wrap removed, which most closely mimicked the physical property of human carotid artery adventitia, for re-creation of the adventitia.

Preparation of the carotid specimen. Human carotid plaque specimens (n = 24) were obtained from patients undergoing standard carotid endarterectomy procedures for clinically significant stenosis of the carotid bifurcation. The surgical technique used for carotid endarterectomy is described in detail elsewhere.[11] Endarterectomy specimens were removed as casts of the carotid bifurcation vessels devoid only of the adventitia and were kept circumferentially intact (Fig. 2*A*). The excised specimens were encased in an ePTFE wrap (6, 7, or 8 mm thin wall ePTFE; W. L. Gore and Associates) in an effort to re-create a structural adventitia (Fig. 2*B*). The outer reinforcing wrap of the encasing ePTFE graft was removed and stretched with surgical clamps to approximate the size of the outer diameter of the plaque. The distal half of each ePTFE covering was cut open longitudinally, and the plaque specimen was inserted into the lumen of the graft. The size discrepancy between the internal carotid and the common carotid arteries was managed by means of trimming and suturing the redundant ePTFE with CV-7

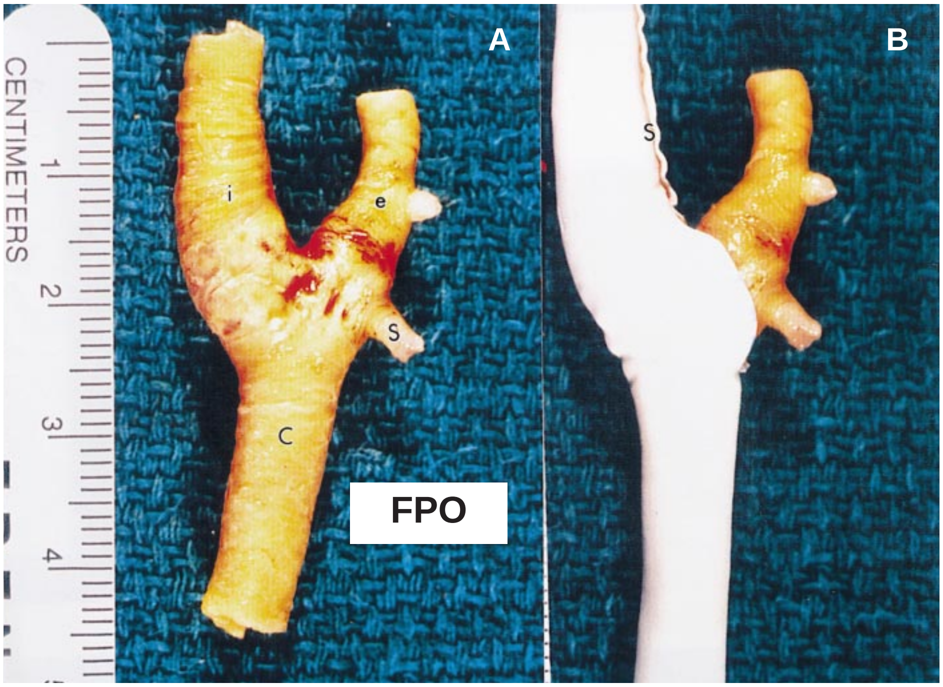

Fig. 2. A, Specimen of human carotid plaque. Specimens are removed as casts of the carotid bifurcation and were kept circumferentially intact. *i,* Internal carotid artery; *e,* external carotid artery; *c,* common carotid artery; *s,* superior thyroid artery. B, Expanded PTFE wrapped specimen. The distal half of the ePTFE graft is cut longitudinally, and the plaque is inserted into the graft. Redundant ePTFE material covering the internal carotid plaque portion is trimmed and sutured with CV-7 sutures (*s*).

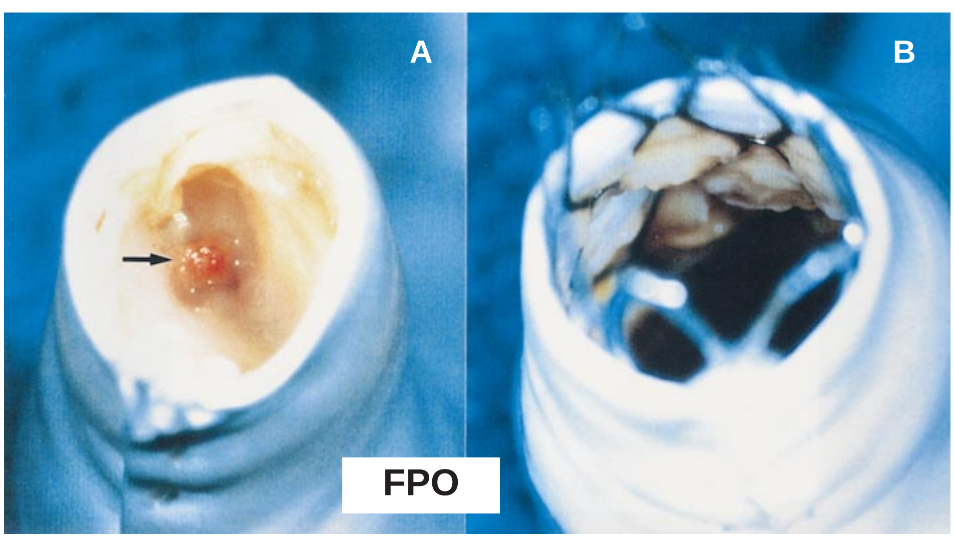

Fig. 3. A, Distal view retrograde into the internal carotid artery. There is no constriction of the plaque by the wrap or any space between the plaque and the ePTFE covering. Mural thrombus is seen at the distal end of the stenosis (arrow). B, Distal view of the same internal carotid plaque specimen after balloon angioplasty and stenting (Palmaz stent).

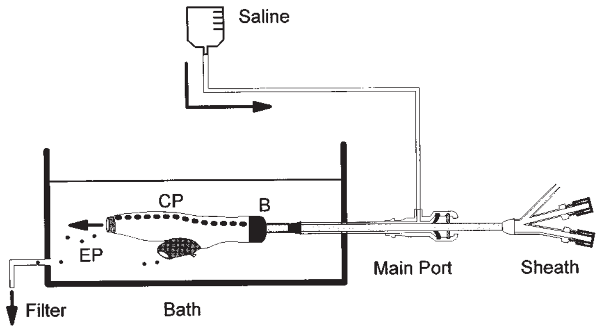

Fig. 4. Schematic of ex vivo apparatus and bath. The ePTFE-covered plaque (*CP*) is connected to a custom-made sheath by means of inflation of the latex balloon (*B*). This plaque-sheath complex is connected to the main port of the bath. A saline bag raised to 130 cm above the bath is connected to the flush channel of the main port to maintain continuous flow through the lumen of the specimen (*arrows*). A sheath with a three-way valve at the proximal end is inserted into the center channel of the main port. This allows insertion of various endovascular imaging and interventional devices. The effluent is drained through a filter to collect the embolic particles (*EP*) generated during the endovascular procedure.

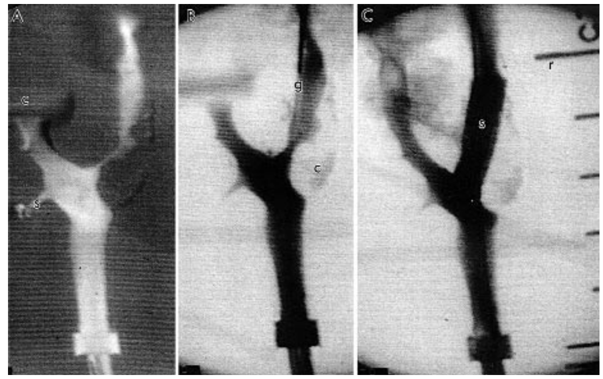

Fig. 5. A, Ex vivo angiogram before intervention (roadmap image), which reveals ulcerated plaque with high-grade stenosis in the internal carotid artery. External carotid artery is temporarily occluded with a clip (*c*) to prevent preferential flow through this vessel. Superior thyroid artery is visualized (*s*). B, Angiogram after balloon angioplasty. Increased luminal diameter is minimal after initial balloon angioplasty. *c*, Calcification on lateral aspect of the plaque; *g*, guide wire. C, Angiogram after stenting. A wide lumen is restored after insertion of a Palmaz stent (P-204) (*s*). *r*, Radiopaque ruler.

sutures (Gore-tex; W. L. Gore and Associates) (Fig. 2*B*). Care was taken to precisely match the size of the ePTFE wrapping to prevent artificial constriction of the plaque (Fig. 3*A*).

Specimens covered with ePTFE were connected to a sheath equipped with a latex balloon at the tip to secure the specimen for subsequent studies (Fig. 4). This specimen and sheath complex was then connected to the inside of a radiolucent plastic bath (Fig. 4). A bag containing isotonic saline solution was positioned 130 cm above the bath and connected to the flush channel of the main port so that continuous saline flow could be maintained through the lumen of the specimen during the entire endovascular procedure. A sheath connected to a three-way valve was inserted into the center channel for endovascular interventions and imaging.

Balloon angioplasty and stenting. Ex vivo angiography of each carotid specimen was performed by means of injection of contrast material into the plaque through the flush valve of the main chamber and imaging with a C-arm fluoroscope (OEC Diasonics Model 9000; OEC Medical Systems, Salt Lake City, Utah) (Fig. 5*A*). A radiopaque ruler was placed beside the specimens to allow accurate angiographic measurement. Recanalization of the specimen was performed with an 0.018 inch steerable guide wire (Hi-Torque Flex-T; Peripheral Systems Group, Temecula, Calif.) with roadmap guidance. Lesions with stenosis greater than 80% were predilated with a 5 mm × 2 cm angioplasty balloon (Ultra-thin Diamond; Medi-tech) or a 3 mm × 2 cm coronary balloon (Scimed, Maple Grove, Minn.) before stenting. Balloon dilation was performed up to a pressure of 7 atm for 30 seconds. Angiograms were obtained after each balloon dilation (Fig. 5*B*). Carotid plaque specimens received either Palmaz balloon-expandable stents (P104, P154, P204, P294; Cordis, Warren, N.J.) or self-expanding Wallstent endoprostheses (8 mm × 5 cm; Schneider, Minneapolis, Minn.). After stent deployment, completion angiography and intravascular ultrasound examination were performed to confirm adequate stent deployment (Fig. 5*C*). Incomplete stent deployment was managed with additional balloon dilation.

Collection and analysis of embolic particles. A continuous flow of saline solution was maintained through the specimen throughout all endovascular procedures. The effluent was collected and filtered (120 μm) at the conclusion of the intervention. The number, size, and composition of recovered embolic particles were analyzed with a dissecting microscope at magnification 70× (SMZ-U; Nikon, Tokyo, Japan) and in paraffin-embedded histologic sections.

Table I. Univariate and multivariate analyses of variables

Type of analysis	*Percentage stenosis*	*Preoperative symptom*	*Sex*	*Diameter of internal carotid artery*	*Calcification*	*Ulcer*	*Echogenicity*
Univariate	0.043	0.78	0.811	0.917	0.66	0.54	0.012
Multivariate	0.048	NP	NP	NP	NP	NP	0.023

Values are *p* values.
NP, Not performed.

Characterization of carotid specimens. For the purpose of multivariate analysis, carotid specimens were prospectively characterized according to the presence of clinical symptoms before endarterectomy and specific findings on angiographic images and duplex ultrasonographic scans (Table I). These characteristics have been shown to play a role in the natural history of carotid disease and to correlate with the outcome of carotid endarterectomy.[7,12-17]

Percentage stenosis was calculated with the following formula: Stenosis = $\{1 - [(MLD - OD) \div OD]\} \times 100$, where MLD is the minimal luminal diameter measured on the ex vivo angiogram before intervention and OD is the outer diameter of the internal carotid plaque.

The presence or absence of plaque ulceration and calcification was determined by means of evaluation of angiograms and plain fluoroscopic images. The presence of plaque echogenicity was determined at preoperative duplex studies obtained with a high-resolution 7.5 MHz linear scanner transducer. All scans were recorded and subsequently characterized according to the degree of echolucency seen with B-mode scanning. The echo pattern of the plaque-free arterial wall in question was used as a standard because echogenicity may vary from patient to patient. Plaques with an echolucent area ≥50% of the total plaque area were characterized as echolucent plaque (types 1 and 2 according to Geroulakos et al.[18] and Sterpetti et al.[19]), and those with an echolucent area <50 % of the plaque area were characterized as echogenic plaque (types 3, 4, or 5).

Statistical analysis. Continuous variables were described as median and range. Wilcoxon rank sum tests were used to assess univariate associations between total number of particles generated and dichotomous variables (lesion characteristics, Table I). Variables for which analyses resulted in *p* values smaller than 0.2 were incorporated into a multiple regression analysis (SAS for Windows 6.11; SAS, Cary, N.C.). Because the total number of particles generated was not normally distributed, a logarithmic transformation was applied in an attempt to make the distribution approach normality and to meet the assumptions of the analysis. Variables were considered significant if the *p* value was less than 0.05.

RESULTS

Characteristics of plaques. Mean percentage stenosis and diameter of the internal carotid artery were 88% ± 10.7% and 7.5 mm ± 1.9 mm, respectively, (mean value ± SD). Preoperative symptoms, calcification, and ulceration were present in 46%, 42%, and 33%, respectively, of the plaques. Sixty-three percent of the plaques were obtained from men, and 56% were characterized as echogenic plaques.

Technical success and number of particles. Balloon angioplasty and stenting were successfully performed on all but one specimen, in which the plaque and wrapping ruptured after balloon angioplasty and stenting. This plaque contained noncompressible circumferential calcification and did not respond to balloon angioplasty. A good angiographic result (absence of vessel rupture, dissection, and restoration of lumen demonstrated at angiography and intravascular ultrasonography) was obtained for the remaining 23 specimens (Figs. 3*B* and 5*C*). The overall technical success rate for balloon angioplasty and stenting was 96% (23 of 24 specimens).

Embolic particles were obtained in each instance, and the number substantially varied among specimens (median 15, range 2 to 126). These particles were predominantly composed of atherosclerotic debris and some organized thrombus and calcified material (Fig. 6). The mean size of the particles was 338 ± 344 mm (mean value ± SD) and the range was 120 to 2100 μm. The total number of particles generated from each specimen had a close positive correlation with the maximum size of the particles ($r = 0.45$).

Univariate analysis of lesion characteristics. Presence of preoperative symptoms, plaque ulceration or calcification, sex, and diameter of the vessel did not significantly correlate with the number of embolic particles recovered (Table I).

Echolucent plaques produced a significantly higher number of embolic particles (26, range 3 to

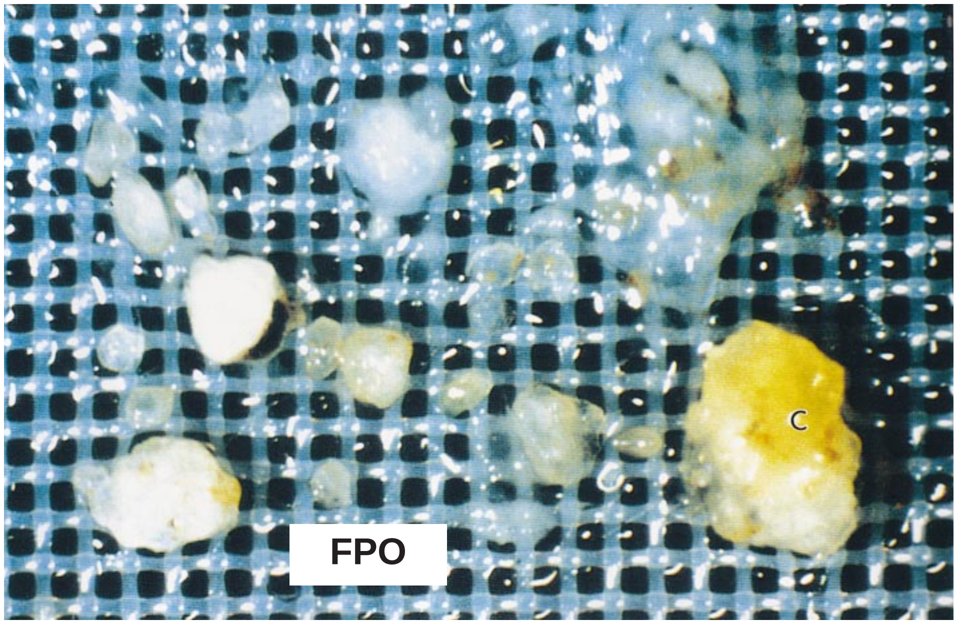

Fig. 6. Macroscopic view of embolic particles generated after angioplasty and stenting. These particles consisted of atherosclerotic debris and calcified material (*c*) (filter size 120 μm; original magnification 40×).

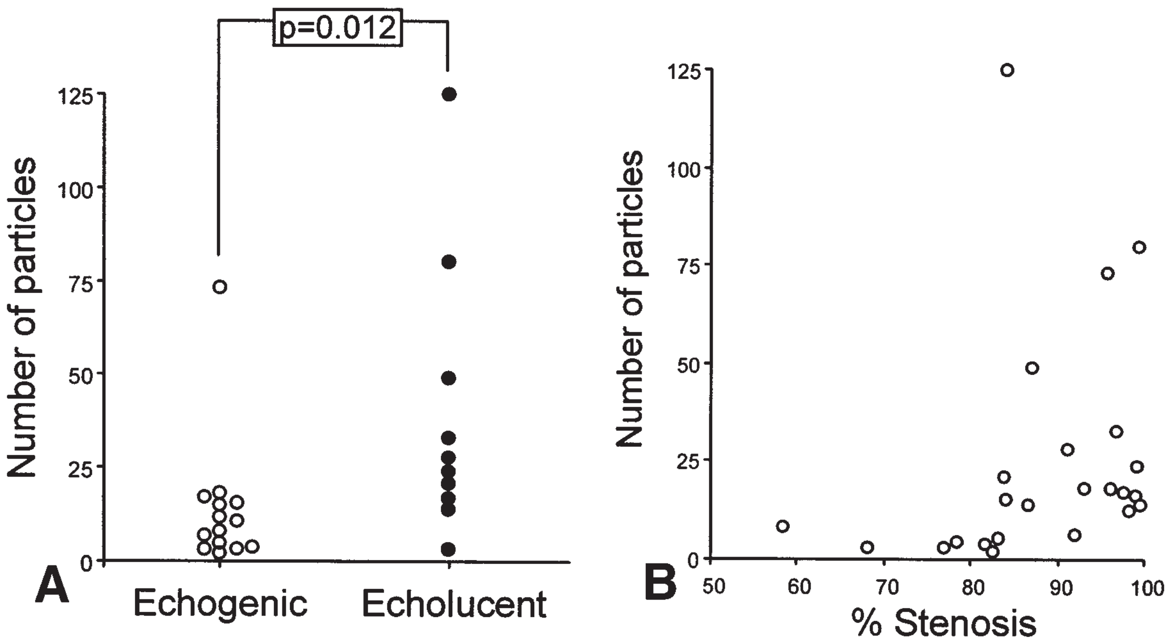

Fig. 7. Quantitative analysis of embolic particles and correlation with variables. A, Echolucent plaques generated a significantly higher number of embolic particles (median 26, range 3 to 126) as opposed to echogenic plaques (median 9.5, range 2 to 73, $p = 0.012$). B, Degree of stenosis correlated with number of particles produced at balloon angioplasty and stenting ($r = 0.55$).

126) compared with echogenic specimens (9, range 2 to 73, $p = 0.012$) (Table I, Fig. 7*A*). In addition, the degree of stenosis correlated with the generation of embolic particles ($r = 0.55$, Fig. 7*B*). Plaques with stenosis ≥90% generated a significantly higher number of particles (17.5, range 6 to 80) compared with those with <90% stenosis (6.5, range 2 to 126, $p = 0.043$; Table I).

Multivariate analysis of lesion characteristics. Multiple regression analysis revealed that echogenicity ($p = 0.023$) and severity of stenosis ($p = 0.048$) were significant independent risk factors (Table I).

DISCUSSION

The purpose of carotid endarterectomy and balloon angioplasty and stenting is prevention of stroke in the treatment of patients with carotid stenosis. Any potential benefits of carotid endarterectomy and balloon angioplasty and stenting in long-term stroke prevention will be offset by high perioperative or periinterventional stroke rates. Because the method by which balloon angioplasty and stenting manage carotid plaque is quite different from that of carotid endarterectomy, we hypothesized that there may exist a unique group of patients who might have a higher periinterventional stroke rate and therefore may not be suitable for this technique. There are several causes of perioperative stroke after carotid endarterectomy, including intraoperative embolic events, acute thrombosis of the carotid artery, and insufficient blood supply during arterial clamping.[19-21] Of these, embolic events are believed to be the most important cause of stroke after balloon angioplasty with or without stenting.[4,22-24] Gil-Peralta et al.[22] performed balloon angioplasty on 82 patients with internal carotid stenosis and reported a perioperative major stroke rate of 5%. Half these strokes were believed to be caused by multiple embolic occlusions of the middle cerebral artery.[22]

This investigation was designed to develop an ex vivo human carotid model to analyze events that may predispose balloon angioplasty and stenting to the devastating complication of embolic stroke. The study demonstrated that a significantly higher number of potential embolic particles were generated from plaques that were echolucent on duplex ultrasound scans. B-mode ultrasonographic scans have been shown to help differentiate gray-level intensities between simple fibrous plaque and those with increased necrotic material.[25] It also has been shown that echogenicity is an important aspect of a plaque and is associated with the presence of symptoms.[18] Sterpetti et al.[19] conducted follow-up studies with patients with plaques of variable morphologic features at duplex examination and found that echolucent plaques (heterogeneous) demonstrated a significantly higher rate of new neurologic events than echogenic plaques. The investigators concluded that plaques with echolucent areas indicate intraplaque hemorrhage and are therefore inherently less stable and prone to fragmentation and embolization than echogenic plaques. Histologic studies have confirmed that these echolucent plaques are predominantly composed of atheromatous debris, lipids, and intraplaque hemorrhage, whereas echogenic plaques mainly consist of more stable fibrous tissue.[19,25-27] In view of the results of these studies, it is not surprising that in our study echolucent plaques produced more particles than fibrous, echogenic plaques after balloon angioplasty and stenting.

This study also showed that the severity of stenosis correlated with the number of embolic particles recovered after balloon angioplasty and stenting. Balloon angioplasty and stenting involve radial compression and fracture of plaque to increase luminal diameter. Higher compression pressures are required to displace plaque within lesions with greater stenoses. It can be expected that a high compression pressure applied to severely stenosed plaque contributed to an increased incidence of embolic particles in our model. Holdsworth et al.[28] reported that the severity of stenosis and echolucency of carotid plaques correlated and that these two variables were dependent factors. Our study did not confirm this, and these two factors appeared to be independent variables for risk for particle embolization.

The clinical significance of the number of embolic particles generated after balloon angioplasty and stenting is not clear. Intuition leads one to believe that patients among whom balloon angioplasty and stenting produced a higher number of particles would be expected to have a higher periinterventional stroke rate than patients among whom fewer particles are produced. Using transcranial Doppler ultrasound, Ackerstaff et al.[20] and Jansen et al.[21] studied the effect of the total number of particles detected during carotid endarterectomy on perioperative neurologic events. In these studies, it was shown that the number of embolic particles detected with transcranial Doppler ultrasound during standard carotid endarterectomy correlated with the rate of subsequent neurologic events.[20,21] Although transcranial Doppler evaluation did not allow accurate identification of particle size, these studies clearly showed the importance of the number of embolic particles in the occurrence of perioperative stroke.

That the number of particles generated closely correlated with the maximum size of the particles in our study further supports the importance of the total number of embolic particles in the occurrence of perioperative stroke.

Balloon angioplasty and stenting are being investigated in several clinical trials, and the feasibility of this technique has been substantiated.[29-33] However, the true safety and long-term efficacy of this procedure have to be better defined. These studies have shown a perioperative stroke or death rate of 5.3% to 8.2%.[29-33] The percentage of patients without symptoms included in these trials ranged from 13% to 72%. Because the perioperative complication rate is highly dependent on the operative indication and patient population being treated, it is difficult to compare these morbidity rates with previously published results of carotid endarterectomy.[12-16] Nevertheless, these initial trials have been criticized because of the high rate of neurologic complications.[23,34] These initial trials had various exclusion criteria, including the presence of calcification, ulceration, and mural thrombus, in an attempt to reduce periinterventional neurologic events.[29-33] Unfortunately, our study showed that none of these factors was a significant risk factor for the generation of embolic particles. Moreover, none of these trials excluded patients with echolucent plaques and plaques with a degree of stenosis greater than 90%, both of which we demonstrated as being independent risk factors for the generation of embolic particles. We believe that if patients with such characteristics are excluded from clinical trials, it may be possible to further minimize the risk for stroke and maximize the potential of balloon angioplasty and stenting for the management of stenosis of the carotid bifurcation.

CONCLUSIONS

Plaques with low echogenicity and those with stenosis ≥90% produced a higher number of embolic particles after ex vivo balloon angioplasty and stenting. Therefore these lesions may be less suitable for balloon angioplasty and stenting with currently used devices. This model can aid in the selection of appropriate patients and in evaluation of the new devices and procedures to minimize procedural complications and maximize the potential for balloon angioplasty and stenting.

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